

REMARKS/ARGUMENTS

Claims 89-107 are active. Claim 89 has been further clarified by reference to page 2 of the specification which describes differences between natural, unmodified deoxyribonucleotides and modified deoxyribonucleotides resistant to nucleases in the human body. Stabilized oligodeoxyribonucleotides are also disclosed on page 7, lines 15-25, of the specification. The term “deoxyribonucleotide” appears on page 2, line 10 of the specification. The new claims find support as follows: claims 94-95 (original claim 6, page 7, lines 26-28), claims 96-97 (original claims 1-2, track prior claims 74-75, page 7, last paragraph), claims 98-101 (track prior claims 77, 79, 80 and 81), claims 102-103 (original claim 8; page 8, lines 11-15), and Claims 104-107 (original claims 9-11, page 8). In view of the above, no new matter is believed to have been introduced. Favorable consideration of this Amendment and allowance of this application are now respectfully requested.

Restriction/Election

The Applicants previously elected with traverse **Group I**, claims 18-24, directed to an ISO comprising an octameric CG motif (AACGTTAT). SEQ ID NO: 18, 19 and 47 which were added during prosecution have been deleted from the new claims. The Applicants reserve the right to file a Divisional Application directed to this or any withdrawn subject matter and remind the Office that 35 U.S.C. §121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, MPEP 804.01.

Rejection—35 U.S.C. §102

Claims 70-73, 78, 89 and 92 were rejected under 35 U.S.C. §102(e) as being anticipated by Mitchell, et al., U.S. Patent No. 6,280,978. Mitchell et al. do not anticipate the invention because they fail to disclose a **stabilized** oligodeoxyribonucleotide (ODN) comprising a nonmethylated octameric CG motif of the sequence AACGTTAT. The oligonucleotides in col. 18 of Mitchell have not been modified to resist degradation by nucleases in the human body as disclosed on page 2, lines 10 to 22 of the specification. Phosphoester linkages occurring in natural, unmodified deoxyribonucleotides are sensitive to the nucleases of the human body. On the other hand, the stabilized ODNs of the invention are resistant to these nucleases and thus suitable for *in vivo* use in humans. Moreover, the claimed oligodeoxyribonucleotides have useful therapeutic (drug) properties immunostimulatory properties by virtue of their higher biological half-lives, and the presence of immunostimulatory non-methylated CG motifs, see the specification, page 3, lines 4-9.

Mitchell et al. disclose an unmodified oligonucleotide. This 24 bases oligodeoxyribonucleotide (ODN) has the sequence TCGAGCAAACGTTATAAATAATGTTC (column 18, lane 54, SEQ ID NO: 6). The ODN disclosed by Mitchell et al., is an oligonucleotide spacer (spacer S) which is hybridized with a complementary oligonucleotide (spacer AS) to form a double-stranded linker which is ligated into a linearized plasmid to generate a pre-trans-splicing molecule (see column 18, lanes 51 to 56). This oligonucleotide is an **unmodified ODN** having the sequence SEQ ID NO: 6 which is used *in vitro*, in general molecular biology and recombinant DNA procedures, but not therapy.

Stabilized ODNs have modifications of the phosphoester bound (phosphorothioate, methylphosphonate) or of the 5' or 3' end which are not compatible with the standard molecular biology and recombinant DNA techniques described by this document (e.g.,

ligation, restriction enzyme digestion) in which the ODN disclosed by Mitchell et al. is used (see column 18, lines 52 to 56 of Mitchell et al.). Mitchell et al., do not disclose chemical modification of the modified oligodeoxyribonucleotide SEQ ID NO: 6 to stabilize it and make it resistant to the nucleases of the human body or contemplate its therapeutic use (e.g., for cancer treatment) Mitchell also provides no motivation for stabilizing this sequence for use as a therapeutic agent, nor any expectation of success that this sequence would have anti-tumor effects when administered to a subject. Accordingly, this rejection may now be withdrawn.

Rejection—35 U.S.C. §102

Claims 70-75, 78-90, 92 and 93 were rejected under 35 U.S.C. §102(e) as being anticipated by Krieg, et al., U.S. Patent No. 6,218,371. Krieg et al. do not disclose a stabilized oligodeoxyribonucleotide (ODN) comprising a nonmethylated **octameric CG motif of the sequence, AACGTTAT** (stabilized CpG ODN comprising AACGTTAT).

Claim 1 and cols. 1-4 and 6-9 of Krieg describe the motif X_1CGX_2 , wherein X_1 and X_2 are (non-specified) nucleotides (col. 3, lines 18-20) where C and G are unmethylated and which “includes at least 8 nucleotides” (col. 3, line 63). Col. 23, lines 1-13 also describe motifs, but these motifs do not specifically disclose the sequence **AACGTTAT** of the pending claims. Moreover, SEQ ID NO: 6 of Krieg, which is pointed out in the Official Action, is not the same as **AACGTTAT**.

Krieg et al. disclose stabilized CpG ODNs comprising tetrameric (X_1CGX_2 , wherein X_1 is A, G or T and X_2 is C, A or T) or hexameric ($X_1X_2CGX_3X_4$, wherein X_1X_2 is GT, GG, GA or AA and X_3X_4 is TT, CT or GT) nonmethylated CG motifs (first paragraph of column 23) which are different from the nonmethylated octameric CG motif AACGTTAT of the pending claims. In addition, none of the ODN sequences disclosed by Krieg et al. (see Table

1, column 39-42) comprise an octameric motif having the sequence AACGTTAT. For example, the sequence SEQ ID NO: 11 comprises AACGTTCT, the sequence SEQ ID NO: 49 comprises AACGTTCC, and the sequence 52 comprises AACGTTGA. The Official Action does not point out any sequence in Krieg that is exactly the same as the sequence required by the present claims and present no reasoning why one of skill in the art would immediately envisage this particular sequence from the broad disclosure of Krieg. Accordingly, this rejection should now be withdrawn.

Rejection—35 U.S.C. §103

Claims 70-76 and 78-93 were rejected under 35 U.S.C. §103(a) as being unpatentable over Krieg, et al., U.S. Patent No. 6,218,371 as applied to claims 70-75, 78-90, 92 and 93, and further in view of Schwartz, et al., U.S. Patent No. 6,562,798. Krieg has been addressed above and does not disclose the specific deoxyribonucleotide sequence required by the pending claims. Moreover, it provides no suggestion to specifically select this sequence, nor any reasonable expectation of success for the superior properties of this sequence. The selection of the two additional bases adjacent to the 3' of the 5'-purine-purine-CG-pyrimidine-pyrimidine-3' is important for obtaining anti-tumor activity and is not a trivial choice.

Krieg et al. does not render the invention obvious, because it does not suggest the motif AACGTTAT required by independent claim 89 nor provide a reasonable expectation of success that a deoxyribonucleotide containing this motif would have antitumoral activity.

Krieg discloses stabilized CpG ODNs comprising tetrameric (X_1CGX_2 , wherein X_1 is A, G or T and X_2 is C, A or T) or hexameric ($X_1X_2CGX_3X_4$, wherein X_1X_2 is GT, GA, AA, GG and AT and X_3X_4 is TT, CT, TC, CC and AT) motifs (first paragraph of column 23). Krieg et al. teach only that the CpG ODN do not contain a CCGG quadmer or more than one

CCG or CGG trimer at or near the 5' and/or 3' terminals (middle of second paragraph of column 23). Krieg et al. teach that preferred CpG ODNs have the sequence 5'TCN₁TX₁X₂CGX₃X₄ 3' in which N₁ has 0 to 25 nucleotides (end of first paragraph of column 23). Furthermore, Krieg et al. teach that two CpG oligonucleotides (TCTCCCAGCGTGCGCCAT and TCCATGACCGTTCCTGACCGTT) which have CpG motifs totally different from AACGTTAT have an antitumoral effect (example 5). Therefore, Krieg et al. cannot suggest or provide a reasonable expectation of success for the functional properties of the invention.

Schwartz does not remedy the deficiencies of Krieg, because it also does not suggest selecting the motif AACGTTAT required by independent claim 89 nor provide a reasonable expectation of success that deoxyribonucleotide containing this motif would have antitumoral activity. Schwartz et al. involve immunostimulatory oligonucleotides having a different immunomodulatory sequence with a modified cytosine and without any antitumor activity.

Therefore, the Applicants respectfully submit that this rejection may be withdrawn, since the prior art does not suggest or provide a reasonable expectation of success for a stabilized oligodeoxynucleotide comprising at least one nonmethylated octameric CG motif of the sequence AACGTTAT. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Rejection--Obviousness-type Double Patenting

Claims 84-88 and 93 were rejected under the judicially-created doctrine of obviousness-type double patenting over claim 1, 3, 4, and 6-9 of U.S. Patent No. 7,108,844. The Applicants respectfully traverse this rejection for the reasons of record. In the event that this ground of rejection is maintained, the Applicants respectfully request that this rejection

be held in abeyance pending the identification of otherwise allowable subject matter. At that time, if necessary, a terminal disclaimer may be filed.

Objection

Claim 73 was objected to as being in improper dependent form. This objection is now moot.

Allowable Subject Matter

The Applicants thank Examiner Zara for indicating that the subject matter of claim 77 is allowable. This subject matter now appears in claim 98 which has been presented as an independent claim and which omits the SEQ ID NOS: 18, 19 and 47 which were objected to as corresponding to non-elected subject matter withdrawn from examination.

Notices of References Cited (PTO-892)

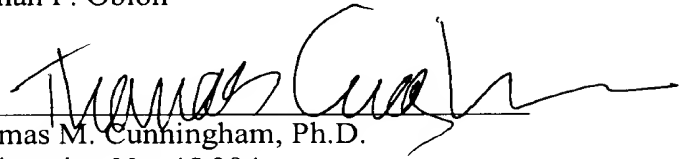
The Applicants believe there is an omission in the "Notice of References Cited". The Applicants respectfully request that Mitchell et al., US Patent 6,280,978, be formally made of record on PTO-892.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Thomas M. Cunningham, Ph.D.
Registration No. 45,394

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/07)